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# IDENTIFICATION OF DISEASE GENES FOR RARE AUTOSOMAL RECESSIVE EPILEPTIC SYNDROMES BY HOMOZYGOSITY MAPPING

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## ABSTRACT

**Introduction:** The genetics of the most common neurological disorders, including epilepsy, with mendelian inheritance has been dissected in the last twenty years. However the genetic etiology of some rare epileptic conditions is still unknown. This research project focuses on rare autosomal recessive (AR) epileptic conditions. The genetic data obtained so far indicate that about half of cases affected by autosomal recessive disorders carry a homozygous mutation descending from a unique ancestor (founder effect). The putative mutation is contained within a segment of the DNA, called "identical by descent" (IBD), that is transmitted along the generations. This segment is characterized by a set of contiguous homozygous polymorphisms (SNP) and may be detected using a genome wide genotyping approach, namely the "homozygosity mapping" which allows the typing of a great number of SNP in order to detect very small IBD segments. Thus nuclear families (sib-pairs) originating from restricted areas can be genotyped in order to identify a new AR disease genes. In addition the novel sequencing methods can further follow up these regions allowing the rapid screening of hundreds genes.

**Material and methods:** Families with at least two affected siblings affected by a rare epileptic condition sharing the same clinical pictures have been selected. Parental ancestors should have originated from the

same geographical area. The affected relatives, their parents and unaffected siblings have been genotyped using the Axiom Genome wide human assay (Affymetrix). A classical linkage analysis has been performed in case of a negative result from the homozygosity mapping approach for families with more than two affected relatives. Homozygosity regions have been then analyzed using a classical Sanger sequencing or using a next generation sequencing approach.

**Results and discussion:** homozygosity mapping allowed the identification of homozygosity stretches in one out of four families. Combined analysis (homozygosity mapping plus linkage) allowed the identification of narrow homozygosity areas in two families. The analysis of the genes included in the isolated stretches is ongoing. The negative result in family 3 and the eventuality of a negative result for the ongoing sequencing analysis can be explained hypothesizing a different inheritance pattern (X-linked, low penetrance heterozygosity, non mendelian and digenic inheritance, compound heterozygousity) or methodology limiting issue (mutation contained in a segment shorter than the homozygosity mapping cut off).

**Key words:** Epilepsy; homozygosity mapping; genetic

# INTRODUCTION

## Genetic and epilepsy

The genetics of most common single-gene neurological disorders has been dissected in the last twenty years. However, the etiology of several rare Mendelian neurological conditions is still unknown with significant implications for diagnosis, genetic counseling and therapy.

Human epilepsy is a common and heterogeneous condition in which genetic plays an important etiological role [1] [2, 3].

The approach to epilepsy genetics has, until relatively recently, been based on Mendelian genetics, relying on the ascertainment of large pedigrees, linkage analysis of polymorphic markers to established disease-associated loci, and positional cloning within these loci to identify the pathogenic gene mutation [4]. Inheritance is autosomal dominant in many of the familial epilepsy syndromes [1, 5] in which mutations have been identified, with all genes with the exception of LGI1[6], encoding for subunits of ion channels (KCNQ2, KCNQ3, SCN1A, SCN1B, SCN2A) [7-10] or neurotransmitter receptors (CHRNA4, CHRNA2, GABRG2) [11, 12]. Autosomal recessive inheritance has also been found in many epileptic syndromes. These vary from very severe syndromes such as progressive myoclonic epilepsies (Lafora disease, Unverricht Lundborg disease, sialidoses, ceroid lipofuscinoses etc) [13-15] to milder phenotype syndromes such as autosomal recessive benign myoclonic epilepsy of infancy [16, 17].

## The identification of autosomal recessive disease genes- Homozygosity mapping

So far the identification of genes for autosomal recessive conditions has been constrained by methodological issues such as the shortage of informative families for linkage analysis, the lack of very dense maps of polymorphic markers and the availability of efficient and low-cost platforms for genotyping and sequencing.

The extensive genetic data collected so far on rare Mendelian diseases indicate that up to half of cases affected by autosomal recessive (AR) disorders carry a homozygous mutation descending from a unique ancestor, a phenomenon called "founder effect". The causative mutation is contained within a chromosomal segment which is transmitted along the generations (i.e. identical-by-descent, IBD) and may vary in size according to the number of recombination events occurring during transmission [18, 19]. Thus, as the ancestor is far in the past and number of transmission increases, the size of the IBD segment harboring the mutation decreases. The IBD segment is characterized by a set of contiguous homozygous single nucleotide polymorphisms (SNP) and may be detected by genome-wide genotyping. This approach named "homozygosity mapping" has been applied to large consanguineous families presenting with neurological disorders, where the common ancestor is close and the size of the IBD segment is large enough to be detected by low-density genotyping [19]

[20] [21] [22] [23] [24]. The proximity of the ancestor allowed several IBD segments to be transmitted and thus multiple affected individuals are required to identify that one co-segregating with the disease [19].
The current microarray-based platforms allow the typing of hundreds-thousands to million single nucleotide polymorphisms (SNPs) to detect very small IBD segments originating from very far ancestors [25]. Thus, the study of non-consanguineous nuclear families such as affected sib-pairs originating from geographic isolates may allow the accurate localization of new AR disease genes, indeed the chance to inherit several IBD segments from a far ancestor by chance is low.
In addition the novel sequencing methods (next generation sequencing) [26] [27, 28] allow the rapid screening of hundreds of genes and the identification of large or multiple IBD segments is not a limiting factor toward the identification of the causative mutation.

The main goal of this project is to identify novel genes for rare AR epileptic syndromes by using homozygosity mapping. This study is part of a major European project and has been conducted in collaboration with the “neurodegenerative and muscle disease” laboratory of the Gaslini Institute in Genova, and has been supported by the Current Research Activity of the Gaslini Institute.

## MATERIAL AND METHODS

### Families

The selection of families is a critical issue to exploit successfully homozygosity mapping. We focused our strategy mostly on pairs of affected siblings rather than large consanguineous families with multiple affected individuals as such nuclear families are quite common in the clinical practice. This approach hypothesizes that there is a unique homozygous mutation descending from a common ancestor and that this common ancestor should precede the proband(s) by several generations allowing a unique or a few IBD segments of small size to be transmitted. Thus, in order to select a suitable samples for homozygosity mapping we evaluated families with at least two relatives (sib-pairs) affected by a rare classified or unclassified epileptic syndrome of unknown genetic etiology, showing an autosomal recessive pattern of inheritance. Families lacking close consanguinity (consanguinity was accepted further than second generation ancestors) and originating from a restricted geographical region or community (ideally less than 100.000 inhabitants) were the most suitable candidates for this approach, as the disease causative mutation is likely descending from a unique ancestor.

The sib-pairs underwent a full diagnostic work-up to exclude common genetic conditions (Karyotype, array-CGH analysis, Fragile X syndrome). Also they have been screened for the most common genetic conditions that would be differentially diagnosed according to the

clinical picture: for example in case of a progressive myoclonic epilepsy siblings have been screened for Unverricht Lundborg disease, Lafora disease [13], sialidoses, ceroid lipofuscinoses [29], mithocondrial encephalomyopathy with ragged red fibers (MERFF) [14].

Peripheral blood was collected from the probands and their available first degree relatives to obtain high-molecular weight genomic DNA. In addition we obtained DNA samples from at least 50 ethnically-matched controls.

**Genotyping and homozygosiy mapping**

Patients and their first degree relatives have been genotyped by using a high-density SNP array (Axiom Affymetrix GW array plate 675 K). This assay contains 675.000 SNP markers that cover the entire genome. The SNP genotype files have been then uploaded on the *homozygositymapper* application [30] to identify runs of homozygous (ROH) SNPs. Intervals had to meet the limit of at least 100 SNPs or 1 MB in size to be further followed up. This cut-off has been chosen on the basis of recent population studies showing that ROHs shorter than around 1.5 Mb may reflect patterns of ancient origin rather than effects of recent endogamy and may account up to 2-3% of the autosomal genome and that individuals with a common maternal and paternal ancestor in the preceding six generations showed ROHs sized more than 5 Mb[31]. However ROHs larger than 1.5 Mb accounting for 0.2-0.3% of the autosomal genome are also found in the general

population[31]. Thus ROHs were not further followed up in case they were present also in the parents or they were known to be a highly conserved region among the populations (i.e. centromeric region) [31], or present in ethnically matched controls.

In the availability of families with more than two affected siblings or other affected relatives and in case of negative result by homozygosity mapping, we also considered the possibility to run a classical linkage analysis (Merlin) [32]. Since homozygous areas have to be in linkage, while it is not always true the contrary, we also considered to match linkage data with homozygosity mapping data in order to detect ROH (smaller than 1.0 Mb o 100 SNP) segments within linkage areas.

**Brief description of the homozygosity mapping technique**

Once purified genomic DNA has been obtained, this is digested using restriction enzymes and legated to an adaptor support. An allele specific extension is performed by using three different oligos: two are specifically designed to recognize the two alleles while the third is able to recognize the correct position on the array. Fragments are then amplified through a PCR reaction with universal primers and labeled with two different fluorochromes (red and green). Array hybridization and washing is then performed on the dedicated high-density SNP array (Axiom Affymetrix GW array plate 675 K). The fluorescent intensity generated from the beads is detected by a scanner (using the GeneTitan reader scanner)(figure 1a). A red color indicates homozygosity for one allele, a green color indicates homozygosity for the second allele while a yellow color indicates heterozygosity.

Genotype files are then uploaded into the homozygositymapper online application that plots the genome wide homozygosity as bar charts with red bars indicating the most promising genomic regions (figure 1b). Furthermore the GeneDisteller engine provides a candidate gene search in that area [33]

**Sequencing of candidate genes**

If the identified homozygous region(s) harbored less than 20 genes we performed conventional Sanger sequencing to detect point mutations. Alternatively we used the next generation exome sequencing (by using the SureSelectXT target enrichment system) approach to screen large set of candidate genes [27, 28]. This approach select non-synonymous, splice site or indel sequence variants in each of the individuals. Then the result is compared to the exome sequences of healthy controls and database SNP (dbSNP) to exclude common variations.

If the ROHs harbored many genes (hundreds), hypothesis of candidate genes has also been conducted through literature search and database data comparison (***ensemble genome Hg 18 http://may2009.archive.ensembl.org/index.html***).

## RESULTS

Four families recruited at the Epilepsy Centre of the University of Naples Federico II have been included in this study:

### Family 1

This family originates from Naples (see figure 2). It has four out of five siblings affected from Familial Infantile Myoclonic Epilepsy (FIME). This is a recessive idiopathic epileptic syndrome that starts in early infancy showing myoclonic seizures, febrile convulsions, and tonic-clonic seizures (see table 1) [34]. All the affected siblings showed the same clinical picture consistent with this syndrome including negative brain resonance magnetic imaging.

A locus on 16p13 has been mapped for this syndrome[35] but our family did not show any linkage with it. Also this family resulted to be negative for TBC1D24 an ARF 6 interacting protein of unknown function that has been found to be mutated in the same family reported by Zara in 2000[17]

High density homozygosity mapping did not show any homozygous area.

A classical linkage analysis has been then performed since this family offered more than two affected members. A small linkage area on the long arm region of chromosome 1 has been identified. Looking into this area we could isolate a small homozygous area spanning from marker 284 to marker 303 (see figure 3a). A study of the included genes in this area pointed out a single gene, the Regulator of G-protein Signaling 21 (RGS 21, see figure 3b), whose function is only partially

known (involvement in taste signaling)[36]. Even though it does not look a good candidate gene for our family we are now proceeding with a Sanger sequencing of the gene.

**Family 2**

This family originates from Naples (see image 4). The probands (IV:1 and IV:3) are two sisters affected from a Progressive form of Myoclonic Epilepsy with ataxia and mental retardation (see fig.2) [37]. Brain MRI showed a slight cerebellar atrophy for both of them. The clinical picture resembled Unverricht-Lundborg disease (ULD) (see table 2). Laboratory findings and molecular analysis excluded this diagnosis and other possible causes of Progressive Myoclonic Epilepsy/Progressive Myoclonic ataxia (Unverricht Lundborg disease, Lafora disease, myoclonic epilepsy with red ragged fibers, neuronal ceroid lipofuscinoses and sialidoses) [13]. The two cousins (IV:5 e IV:6) presented with a very similar clinical picture.

High density homozygosity mapping analysis did not show any homozygous stretch. However since the blood samples of their first degree affected cousins were available, we performed a classic linkage analysis. One little stretch on chromosomes 2 and four little stretches on chromosome 17 were found (see image 5 and 6). Another little area on chromosome 3 has been discarded since it was also present in their parents. A homozygous mapping has been then performed in these areas. The result from the combined analysis allowed the detection of a small area on chromosome 2 (from marker rs35182736 to marker rs36055280) (see figure 5a) and four small areas on chromosome 17

(from marker rs12051702 to marker rs8074678; from marker rs10971025 to marker rs9754; from marker rs2269858 to marker rs7219346; from marker rs11079043 to marker rs11871636) (see figure 6 a, c, e, g). A list of the included genes is provided in the figure 5b, 6b, 6d, 6f, 6h and in the supplementary data file 1.

These areas harbor totally less than 30 genes. An exome sequencing is undergoing.

**Family 3**

This family originates from Naples (see image 7): the probands are two siblings affected from drug-resistant epilepsy (Lennox Gastaut like), mental retardation, visual failure with retinitis pigmentosa and learning disabilities (see table 3). They also presented with short stature, macroglossia, obesity, precocious puberty, heart hypertrophy, hypothyroidism, partial teeth agenesis, skeletal abnormalities (see image 8). Brain MRI data are not available but they have been reported as normal. The clinical pictures drove the attention to Bardet Biedl syndrome (BBS) even though they were not showing polydactyly nor renal failure (see table 3) [38]. They have been screened for common BBS allele (BBS1 M309R and BBS10 C91fsX95) and they were found to be negative.

High density homozygosity mapping has been performed and the result showed no homozygous areas. In this family linkage analysis was not performed since no other affected members were available.

**Family 4**

This family originates from a small village in Naples (Bacoli; 26500 inhabitants) (see image 9): the probands are two siblings affected from drug-resistant epilepsy (Lennox Gastaut like), severe mental retardation, peripheral neuropathy, psychosis, visual failure and deafness (see table 4). They also presented with short stature, macroglossia, skeletal abnormalities and facial dysmorphisms (see image 10). Brain MRI showed the same abnormalities in both the brothers, namely white matter altered signal in the ventricle posterior area; dysmorphic features of the brainstem and thinning of the corpus callosum. The pedigree of this family showed a consanguineous marriage in the fourth previous generation. This has not been considered as an exclusion criteria since it was further than the third ancestor generation. The high density homozygosity mapping has shown two homozygous stretches, on chromosome 2 (from genomic position 176414781bp to genomic position 243261751bp) and 19 (from genomic position 20799670bp to genomic position 39641146 bp) (see image 11). The area on chromosome 2 harbors 626 genes, while the area on Chromosome 19 harbors 352 genes. The study of the candidate genes through the gene distiller software is undergoing and candidate genes will be sequenced as appropriate.

## DISCUSSION AND CONCLUSIONS

Data reported from this study are heterogeneous reflecting the heterogeneous clinical pictures of the selected families. Overall high density homozygosity mapping allowed the detection of two homozygous stretches in one out of four families (family 4). In family 2 we were able to isolate 5 narrow homozygous areas by combining high density homozygosity mapping and classic linkage analysis. In family 1 a homozygous area has been isolated using classical linkage analysis and studying the haplotype. The genes included in these stretches are under screening through a next generation sequencing approach for family 2 and a classic Sanger sequencing for family 1. We will hopefully find a mutation within the narrowed regions. However a possible negative result need to be taken into account. This possibility can be explained hypothesizing a different pattern of inheritance that cannot be detected by homozygosity mapping (X-linked, low penetrance heterozygosity, non mendelian and digenic inheritance, compound heterozygosity etc). Other possible explanations may include methodology issues (mutations within areas less than 1.0 MB or less than 100 SNP).

We failed to show any area for family 3 which can be explained by one of the previous reasons. Compound heterozygosity seems to be the best explanation. Indeed up to half recessive traits are reported to be coumpound heterozygous [19]. Theoretically a lower SNPs cut-off

could be considered to find out a gene contained in a narrower homozygous area. However ROHs smaller than 1 Mb are too common in the general population and the eventuality to find many ROHs is likely to occur[31]. Also the interpretation of the data would not be easy to address.

In our opinion homozygosity mapping is a valuable tool to analyze nuclear families with siblings affected from the same neurological condition suggesting a recessive inherited trait. Furthermore a combination of different genetic techniques can enhance the likelihood of finding new mutations. Probably a more detailed selection of the criteria would be useful to get more consistent results.

According to the European Organization for Rare Diseases (Eurodis), rare disease (i.e. pathological conditions with population prevalence<1/2000) account for more than 5000 different forms and affects cumulatively about 6-8% of the general population. The etiology of about 80% of these disorders is presumed to be genetic even though in many instances the defects have been not yet characterized. Among these the autosomal recessive epileptic disorders are individually rare, but cumulative are not infrequent and are routinely seen at the Epilepsy Centre of the Federico II University. The phenotypes we selected for this study represent a heterogeneous group characterized by different epileptic conditions, mental retardation, dysmorphisms, slight brain MRI abnormalities and other organs involvement. These conditions show a complex management and raise puzzling clinical issues. The dissection of the genetic etiology is a critical step toward the diagnosis, genetic counseling and in future,

treatment. This ongoing project will hopefully allow the identification of novel disease genes responsible for these unknown clinical conditions and help with their clinical management.

## FUTURE STUDIES

Future studies will be needed to help clarifying the function of these putative genes and consequently the phenotypic spectrum of the conditions. In the future we aim to follow up the putative mutations to assess their pathogenic effect. This will be done using by bioinformatic tools (***endeavor ranking http://homes.esat.kuleuven.be/~bioiuser/endeavour/index.php***) to explore whether they affect an evolutionary conserved aminoacid or a functional domain of the protein or alter its correct folding. Cellular studies will be performed to experimentally evaluate the impact of mutations on cell survival and differentiation and on specific cellular functions by overexpressing wild-type and mutant proteins in neuronal or glial cell lines.

## FIGURES, TABLES AND SUPPLEMENTARY DATA

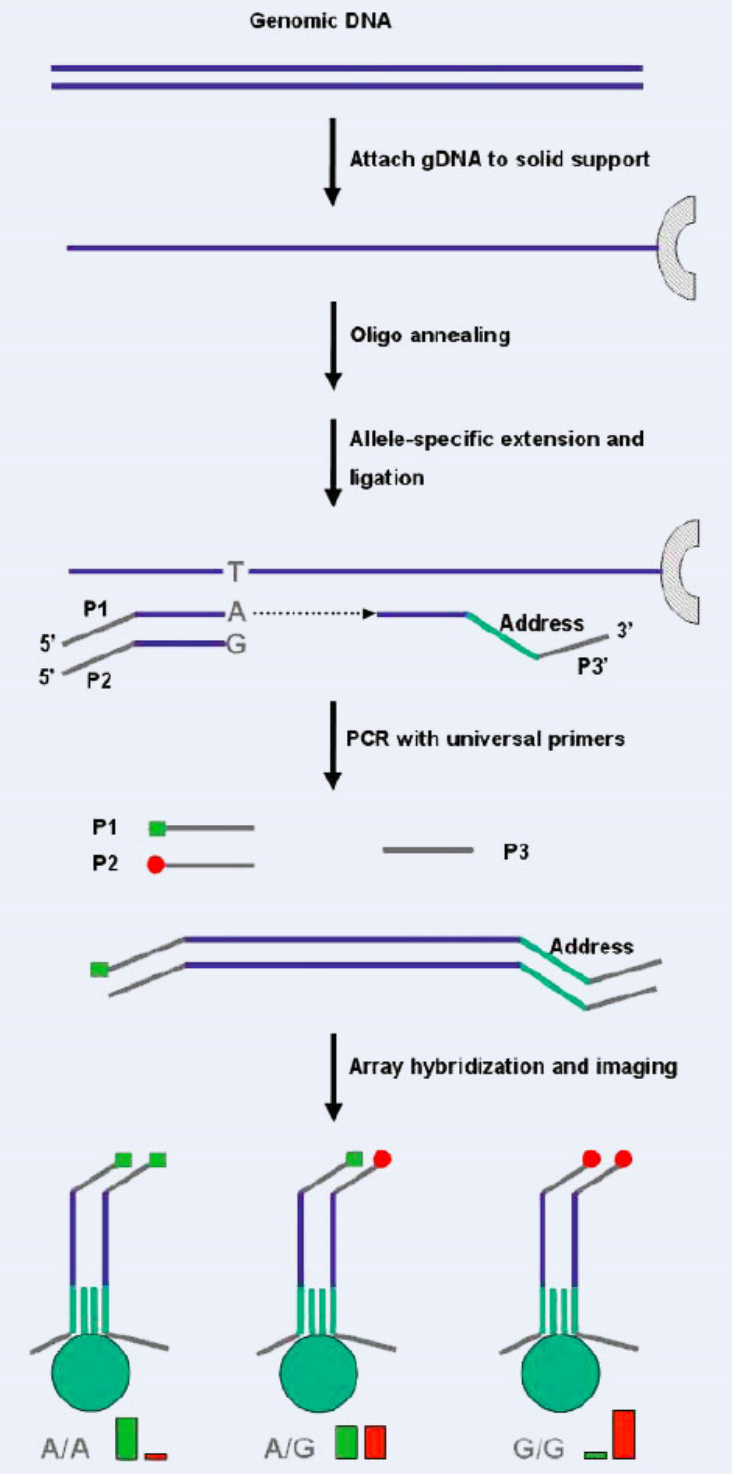


**figure 1a**. homozygosity mapping technique: purified genomic DNA is digested using restriction enzymes and legated to an adaptor support. An allele specific extension is performed by using three different oligos (two recognize the alleles while the third recognizes the position on the array). Fragments are then amplified through a PCR reaction and labeled with two fluorochromes (red and green). After the array hybridization and washing the fluorescent intensity is detected by a scanner. A red color indicates homozygosity for one allele, green color indicates homozygosity for the other allele; yellow indicates heterozygosity.

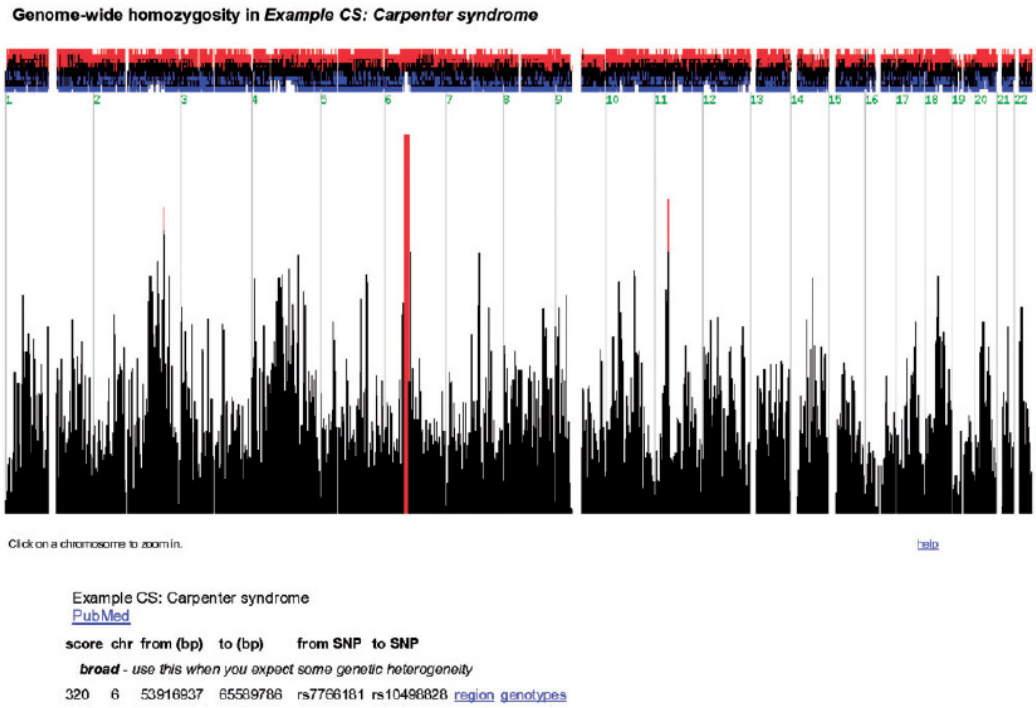


**Figure 1b**: homozygositymapper output. Once genotype files are uploaded into the homozygositymapper online application a genome wide plot is generated with bar charts where red bars indicate the most promising genomic regions

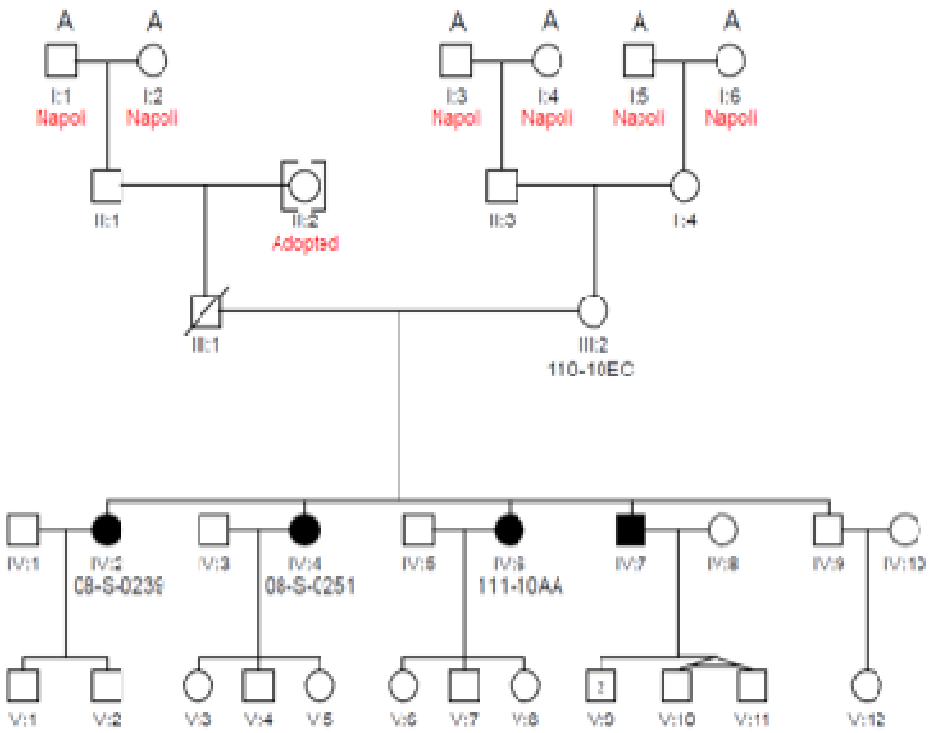


**figure 2**: pedigree of family 1

| Patient ID/ Sex/birth date | Age of onset | Neurological features | Non-neurological features | Neuroimaging | Last follow-up (year) |
|---|---|---|---|---|---|
| IV :2/F/1947 | 13 | Absences+GTCS+ myoclonic | tremor | Normal | 2011 |
| IV:4/F/1948 | 14 | Absences+GTCS+ myoclonic | - | Normal | 2011 |
| IV:6F/1944 | 25 | GTCS | - | Normal | 2011 |
| IV:7/M/1942 | 20 | GTCS | - | Normal | 2011 |

**table 2**: clinical data of family 1; GTCS: generalized tonic-clonic seizures


**figure 3a**: result for family 1. The red square box highlights the homozygous area within the linkage area

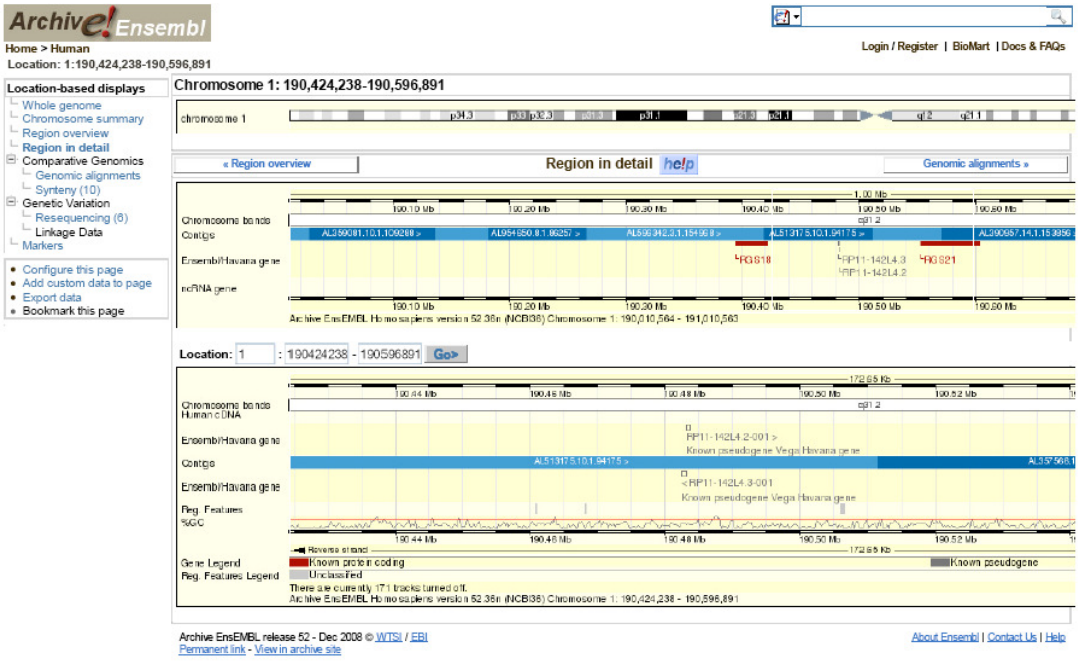


**Figure 3b**: detail of the homozygous area within the linkage area on chromosome 1 from figure 3a containing the gene encoding for the Regulator of G-protein Signaling 21 (RGS 21).

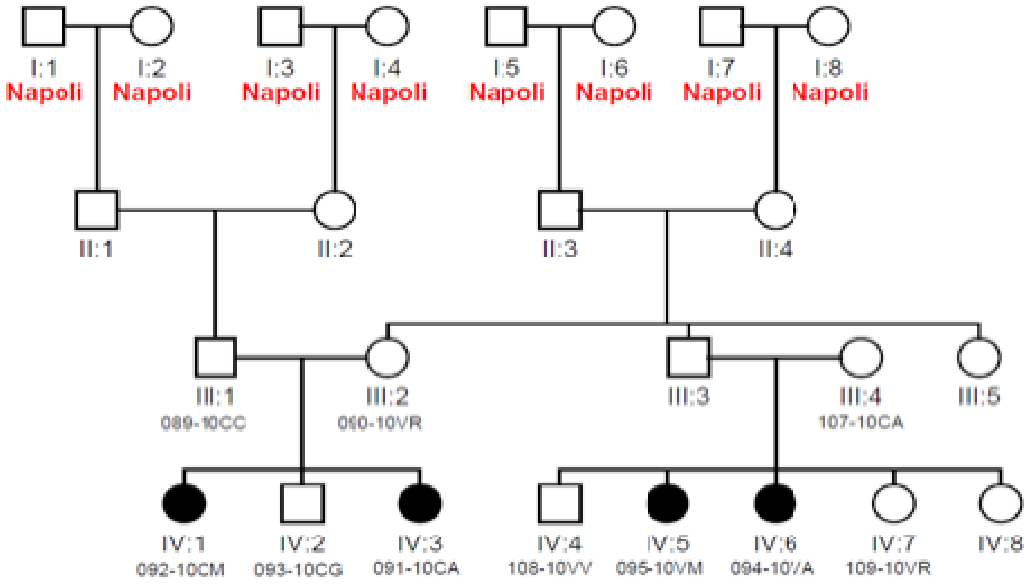


**figure 4**: pedigree of family 2

| Patient ID/ Sex/birth date | Age of onset | Neurological features | Non-neurological features | Neuroimaging | Last follow-up (year) |
|---|---|---|---|---|---|
| IV:1/F/1966 | 12 | Progressive myoclonus, ataxia, mental retardation | - | Slight cerebellar atrophy | 2011 |
| IV:3/F/1973 | 8 | Progressive myoclonus, ataxia, mental retardation | - | Slight cerebellar atrophy | 2011 |
| IV:5/F/1973 | 10 | Progressive myoclonus, ataxia, mental retardation | - | Slight cerebellar atrophy | 2011 |
| IV:5/F/1975 | 10 | Progressive myoclonus, ataxia, mental retardation | - | Slight cerebellar atrophy | 2011 |

**table 2**: clinical data of family 2

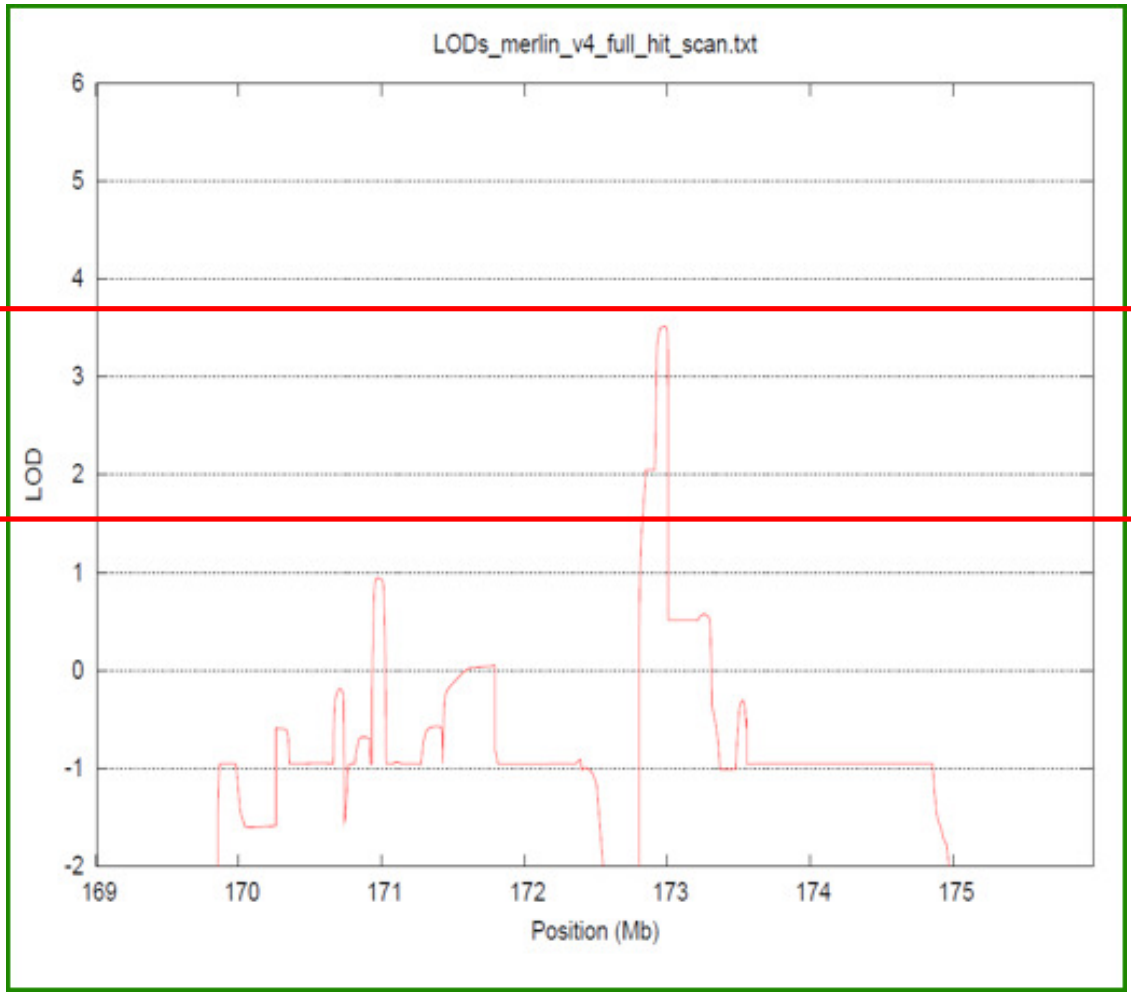


**figure 5**: linkage area on chromosome 2 ( within the red box) for family 2.

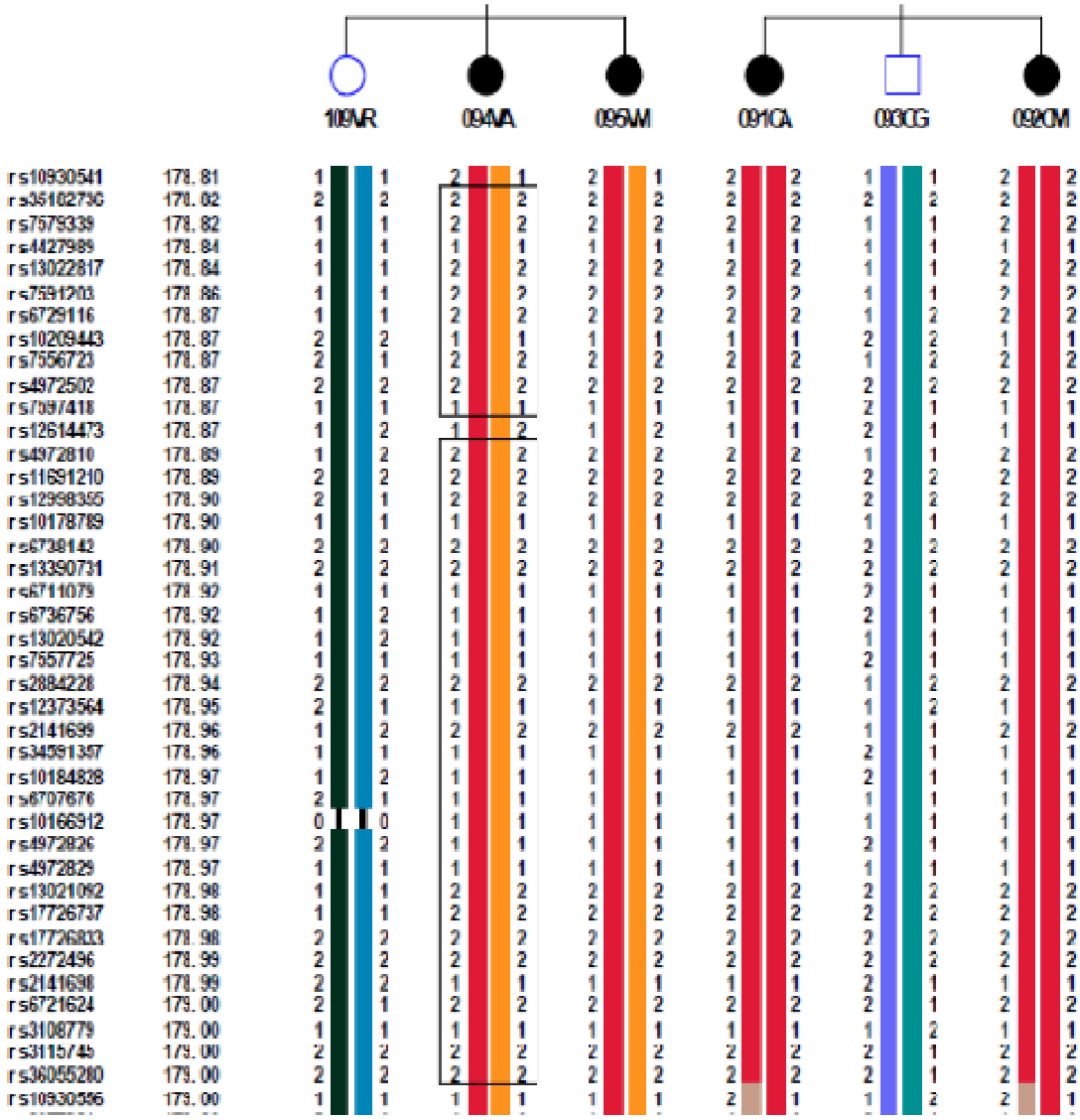


**Figure 5a**: combined analysis (linkage+homozygosity mapping) for family 2 showing a little homozygosity area on chromosome 2 (squared box)

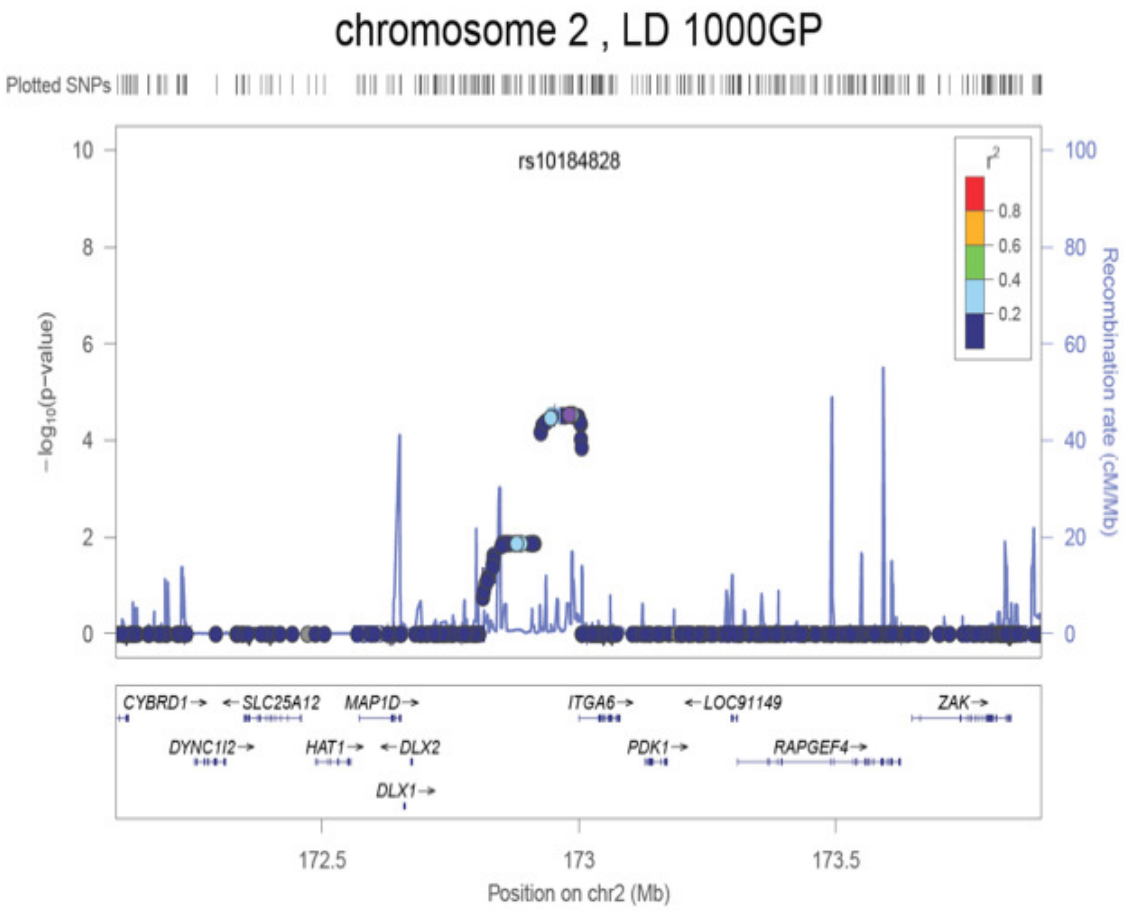


**Figure 5b**: detail of the area in figure 5a showing the included genes

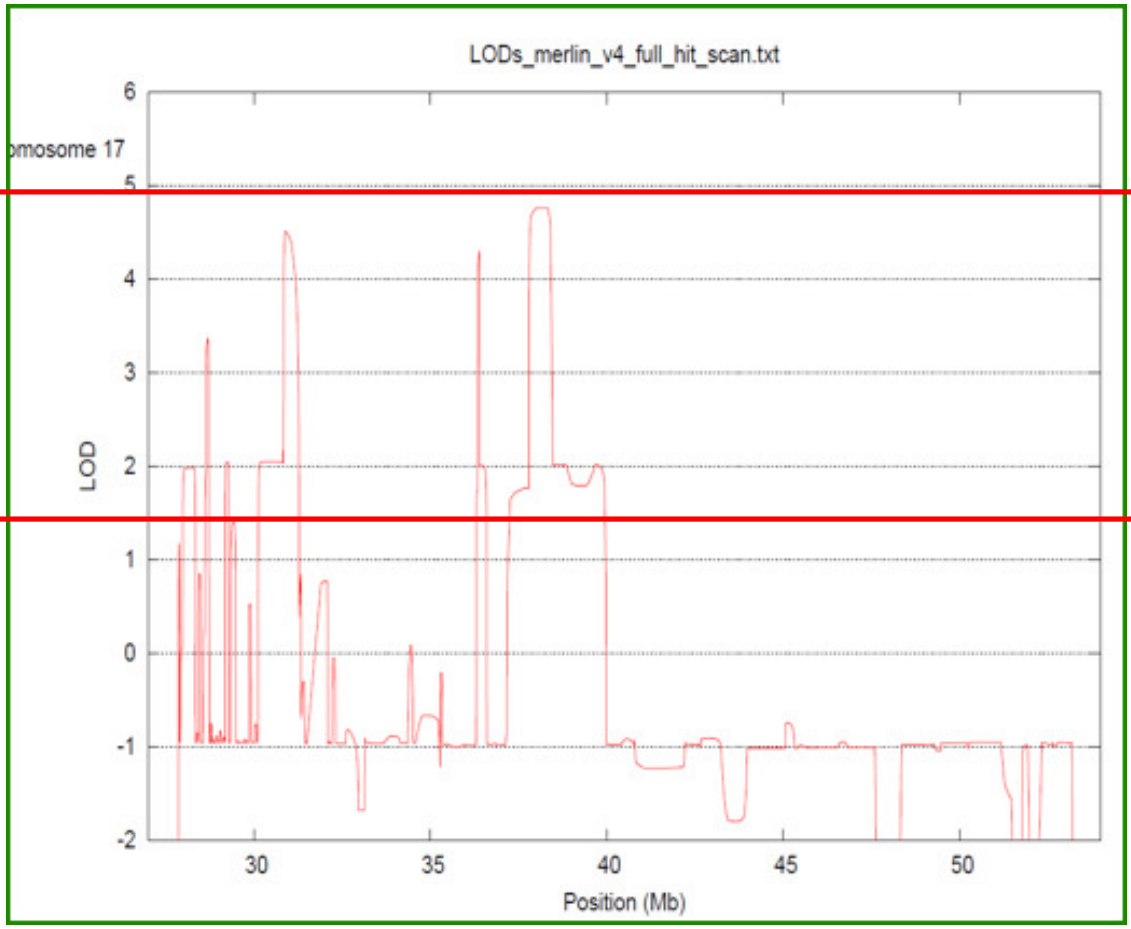


**figure 6**: four linkage areas on chromosome 17 for family 2 (within the red box)

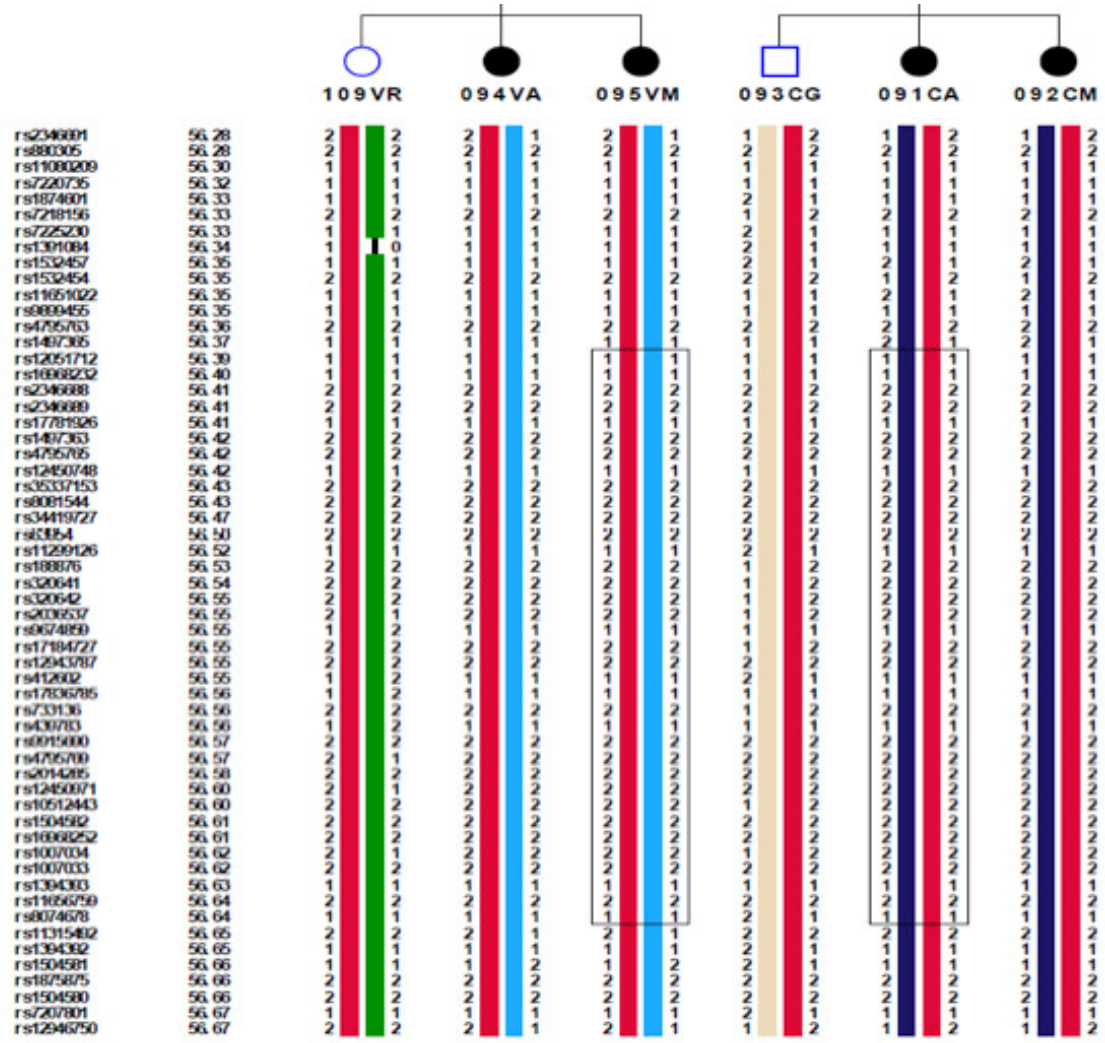


**Figure 6a**: combined analysis (linkage+homozygosity mapping) for family 2 showing a little homozygosity area on chromosome 17 (squared box)

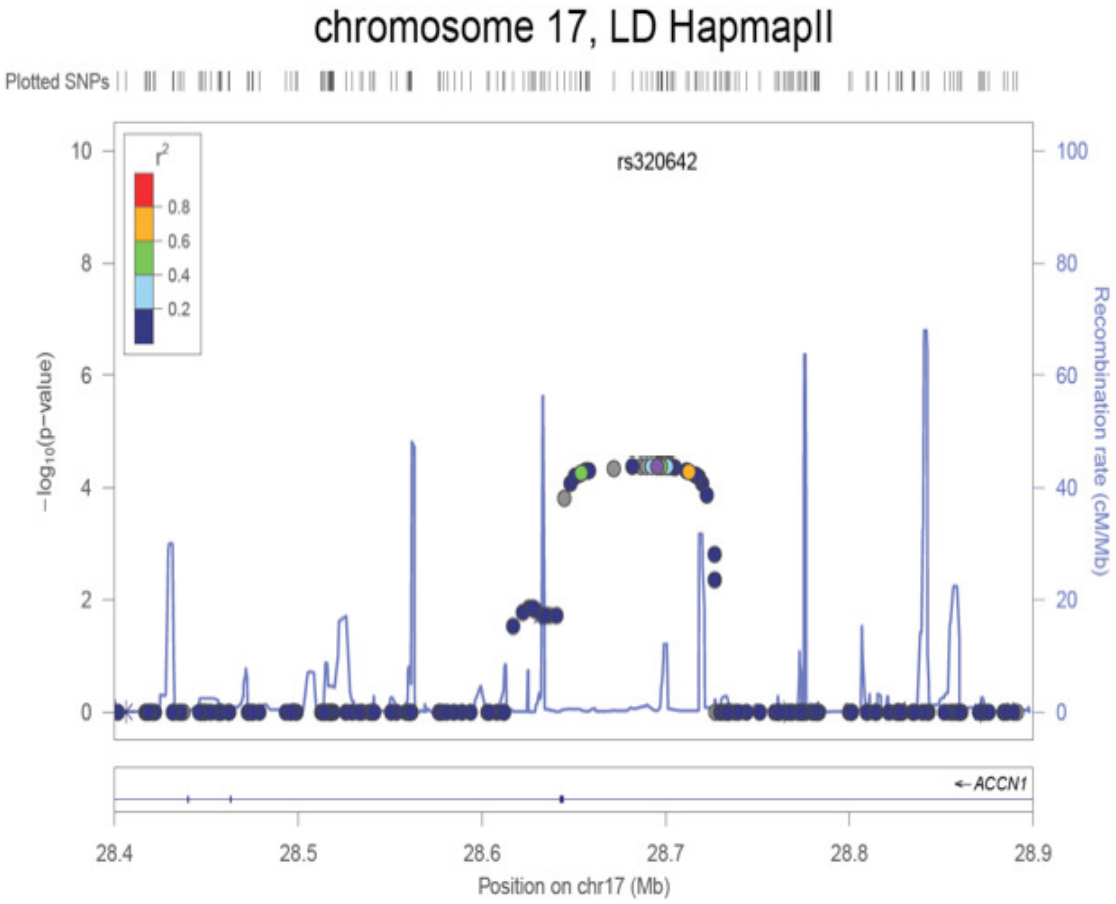


**Figure 6b**: detail of the area in figure 6a.

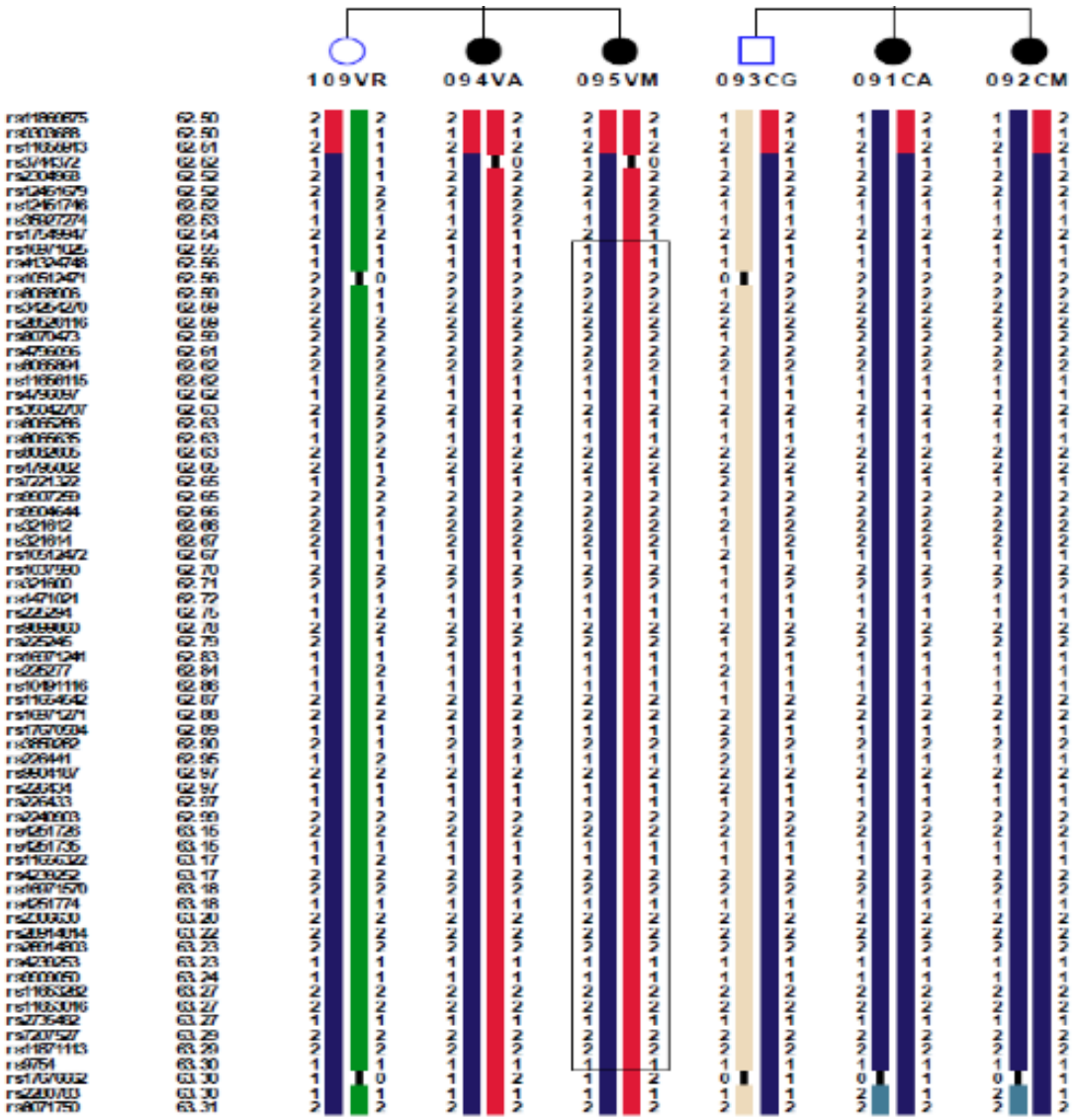


**Figure 6c:** combined analysis (linkage+homozygosity mapping) for family 2 showing a little homozygosity area on chromosome 17 (squared box)

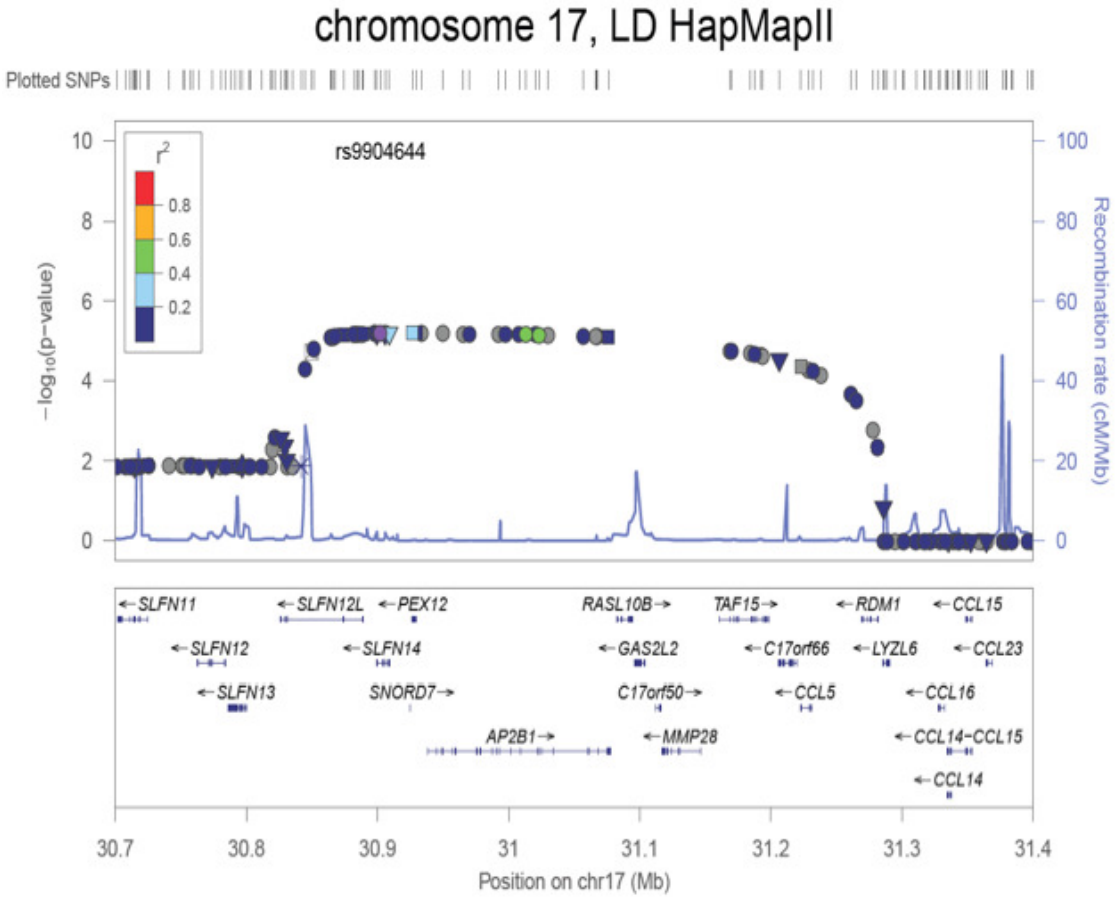


**Figure 6d**: detail of the area in figure 6c showing the included genes

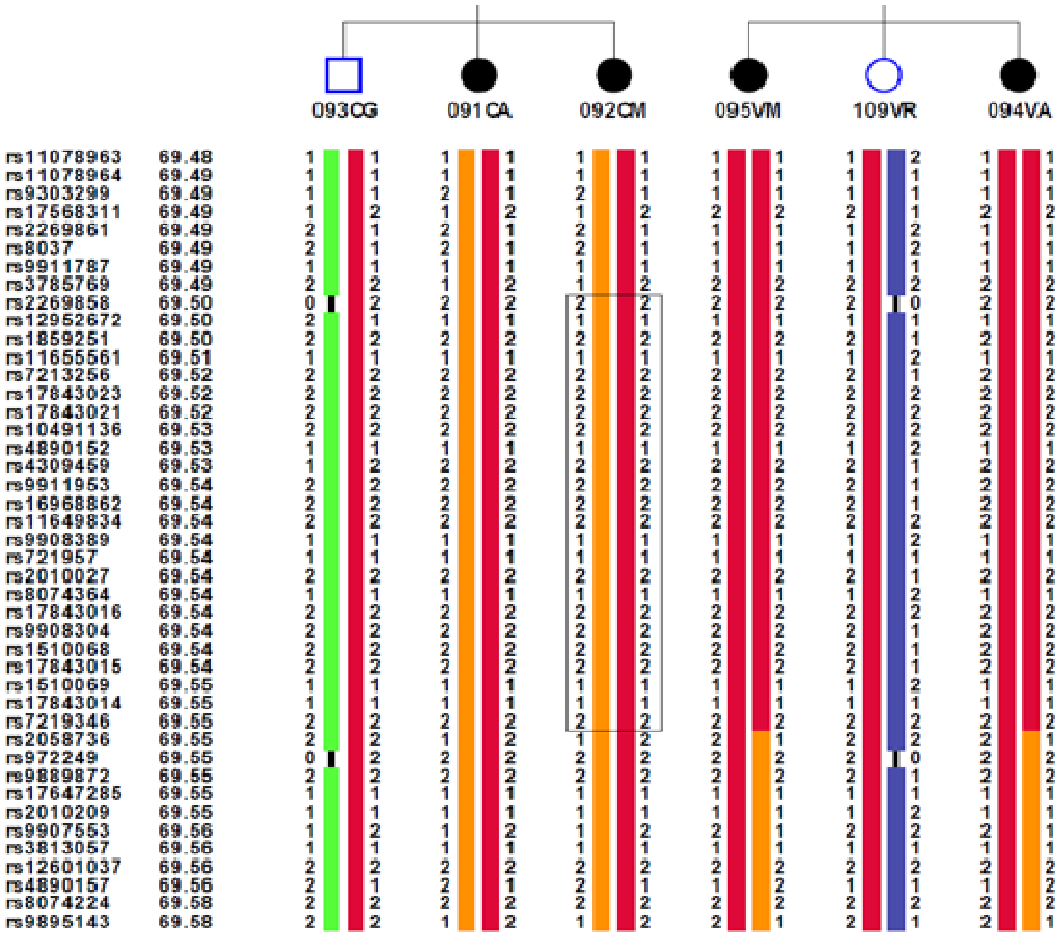


**Figure 6e:** combined analysis (linkage+hom mapping) for family 2 showing a little homozygosity area on chromosome 17 (squared box)

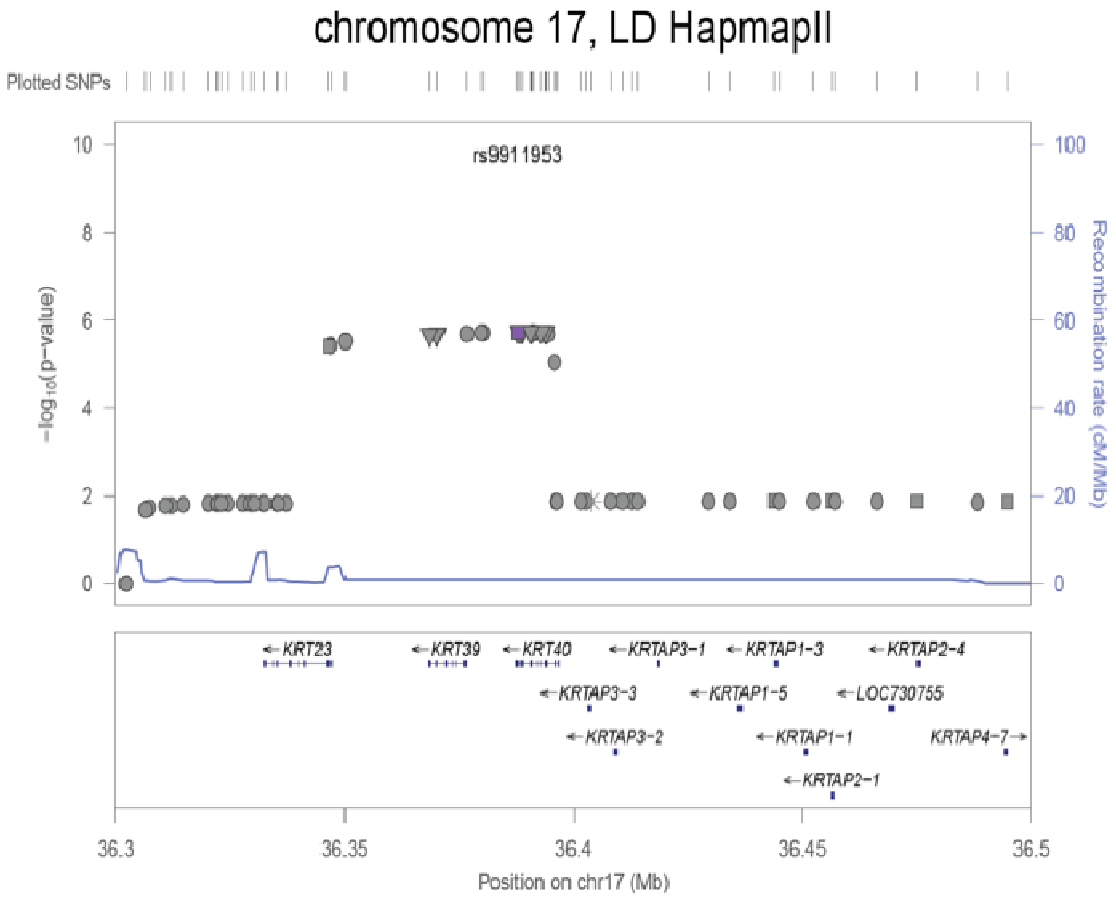


**Figure 6f**: detail of the area in figure 6e showing the included genes

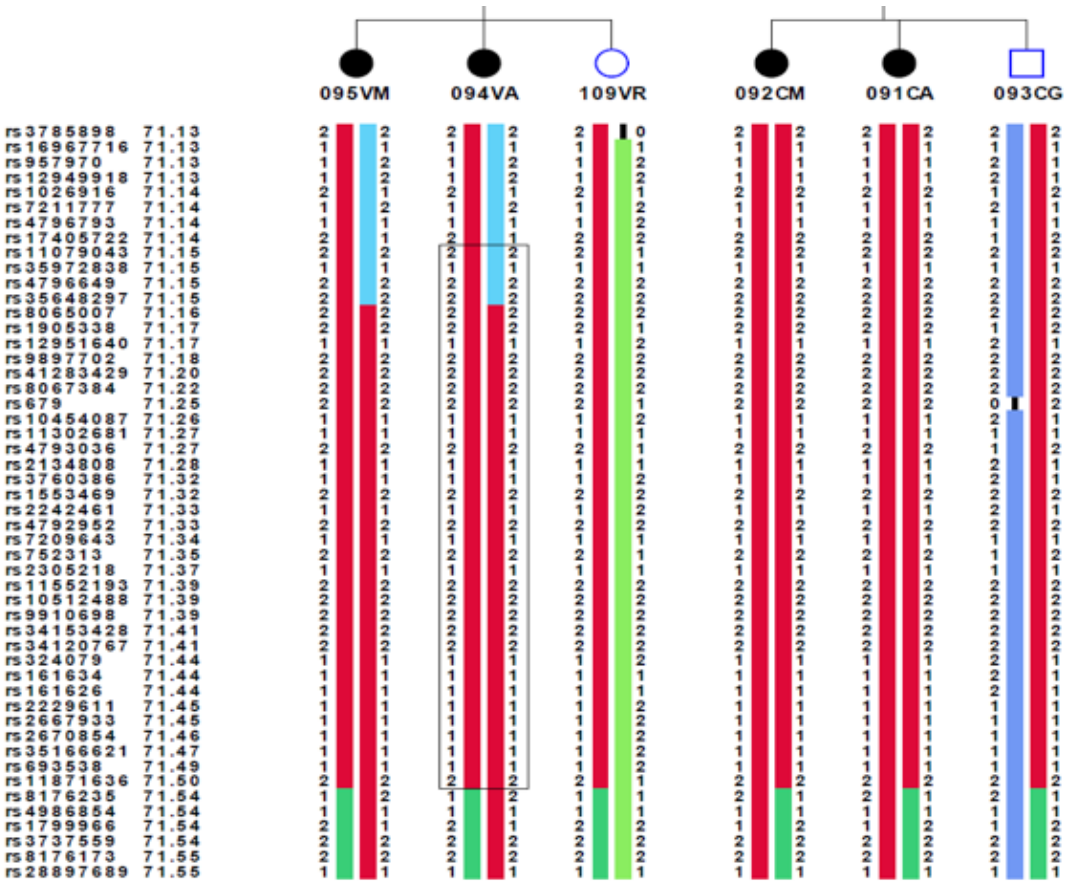


**Figure 6g**: combined analysis (linkage+homozygosity mapping) for family 2 showing a little homozygosity area on chromosome 17 (squared box)

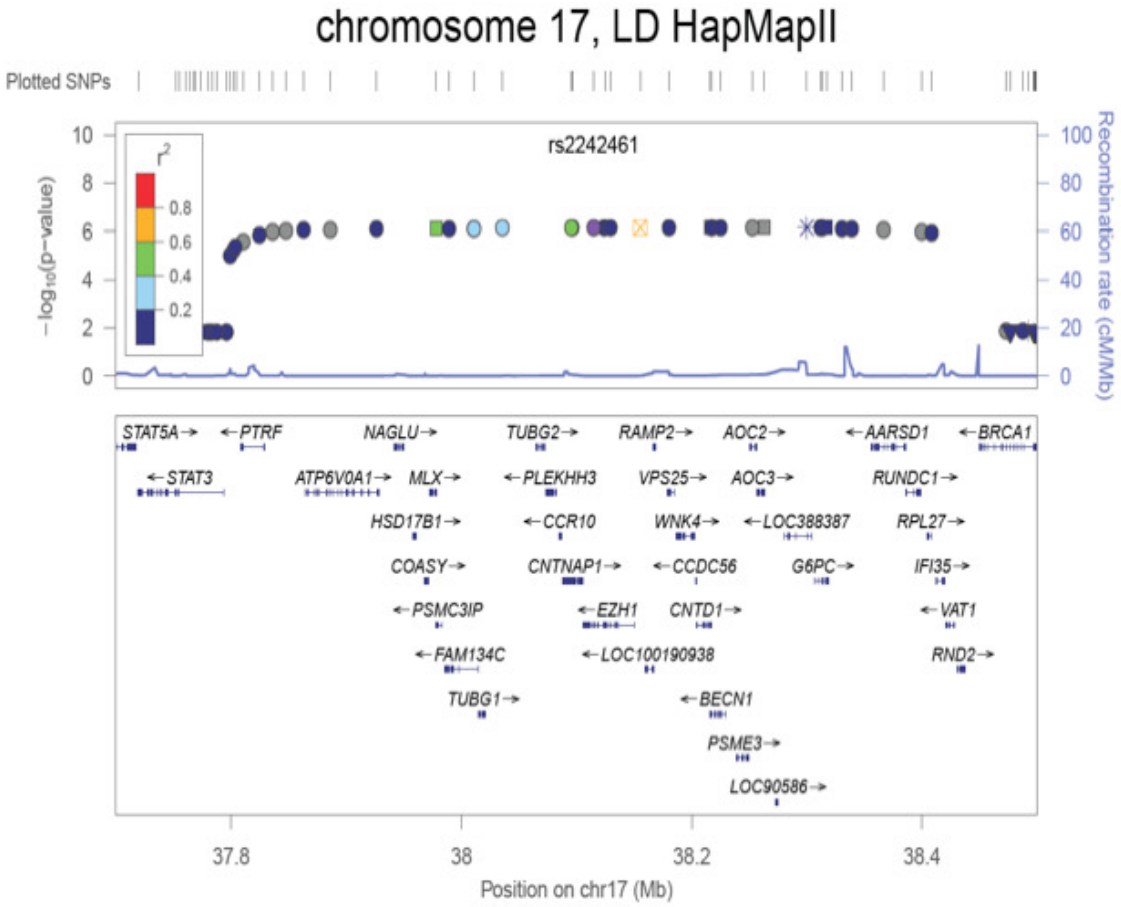


**Figure 6h**: detail of the area in figure 6g showing the included genes

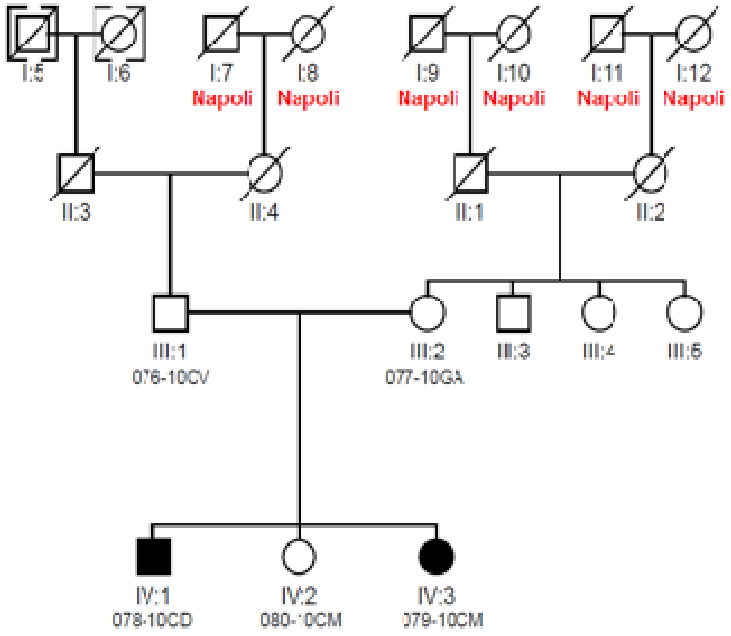


**figure 7**: pedigree of family 3

| Patient ID/Sex/birth date | Age of onset | Neurological features | Non-neurological features | Neuroimaging | Last follow-up (year) |
|---|---|---|---|---|---|
| IV:1/M/1968 | 5(seizures) | Epilepsy, psychomotor delay, learning difficulties, visual failure | Short stature, macroglossia, obesity, precocious puberty, heart hypertrophy, hypothyroidism, partial teeth agenesis, skeletal abnormalities | NA | 2011 |
| IV:3/F/1978 | 7(seizure) | Epilepsy, psychomotor delay, learning difficulties, visual failure | Short stature, macroglossia, obesity, precocious puberty, heart hypertrophy, hypothyroidism, partial teeth agenesis, skeletal abnormalities | NA | 2011 |

**table 3**: clinical data of family 3

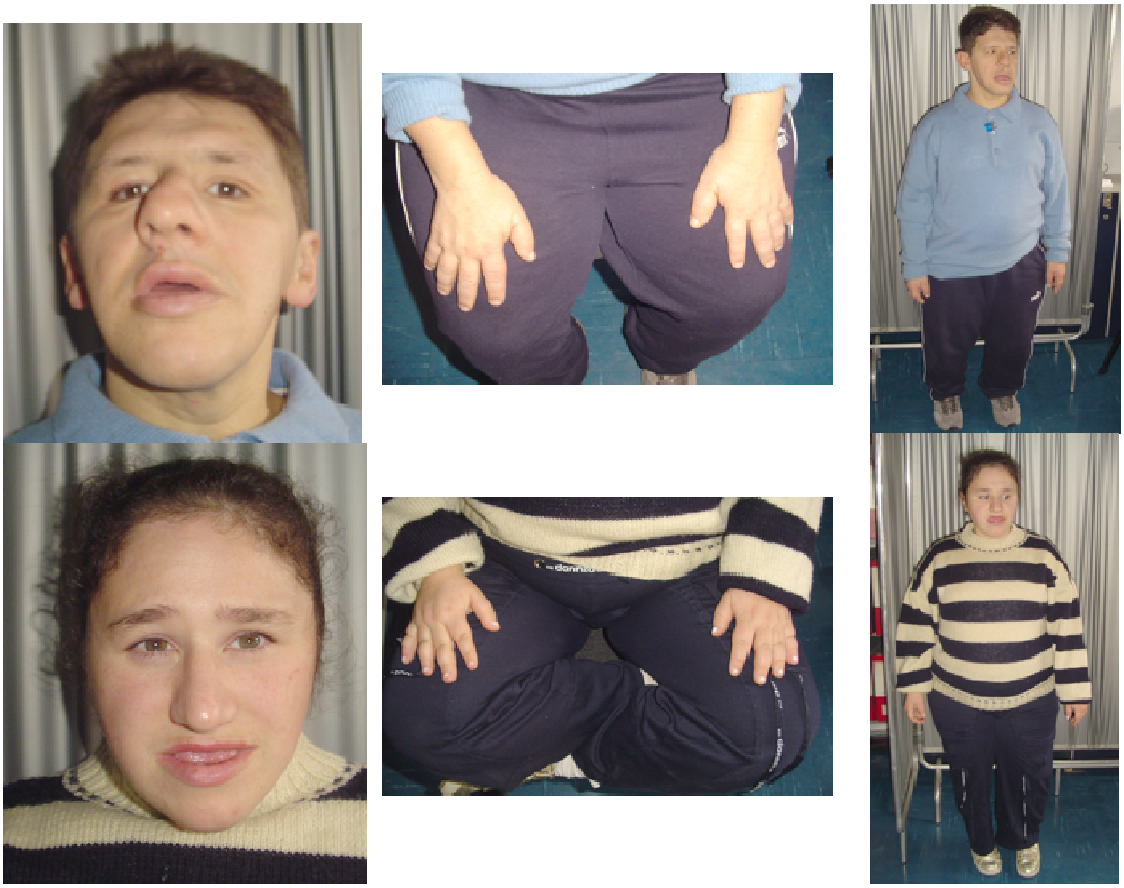

**figure 8**: phenotype of patients IV:1 e IV:3 from family 3 showing facial dysmorphysms (downslanting palpebral fissures, bulbous nose, macroglossia, full lower lip) brachydactyly and short stature.

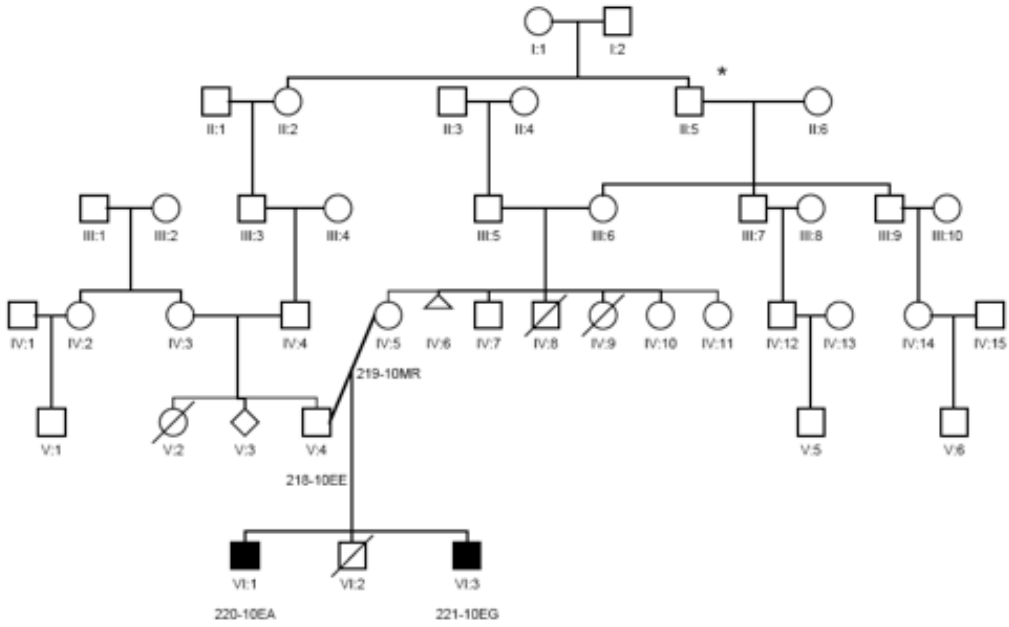


**Figure 9**: pedigree of family 4 showing a consanguineous marriage in the fourth previous generation (asterisk).

| Patient ID/ Sex/birth date | Age of onset | Neurological features | Non-neurological features | Neuroimaging | Last follow-up (year) |
|---|---|---|---|---|---|
| V: 1/M/1991 | - | GTCS; mental retardation | Asymmetric hypotrophy (calves); heart and kidney defects; dysmorphisms | White matter changes; CC hypoplasia | 2011 |
| V: 3/M/1994 | 6m | GTCS; mental retardation | Asymmetric hypotrophy (calves); heart and kidney defects; dysmorphisms | White matter changes; CC hypoplasia | 2011 |

**table 4**: clinical data of family 4. GTCS: generalized tonic clonic seizures; CC: corpus callosum

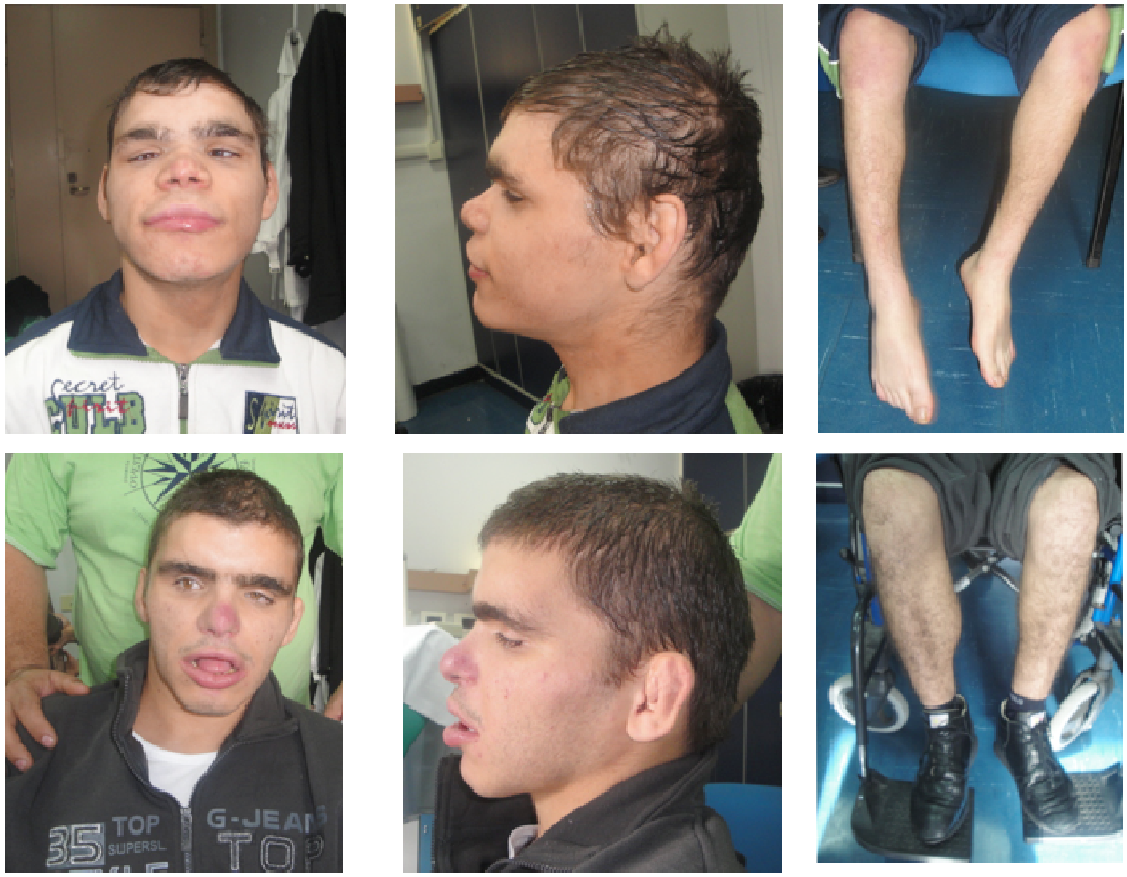

**figure 10**: phenotype of patients IV:1 and IV:3 from family 4 showing facial dysmorphysms (hypertelorism, flat nasal bridge, full lower lip, abnormal pinna folding) and asymmetric hypotrophic calves.

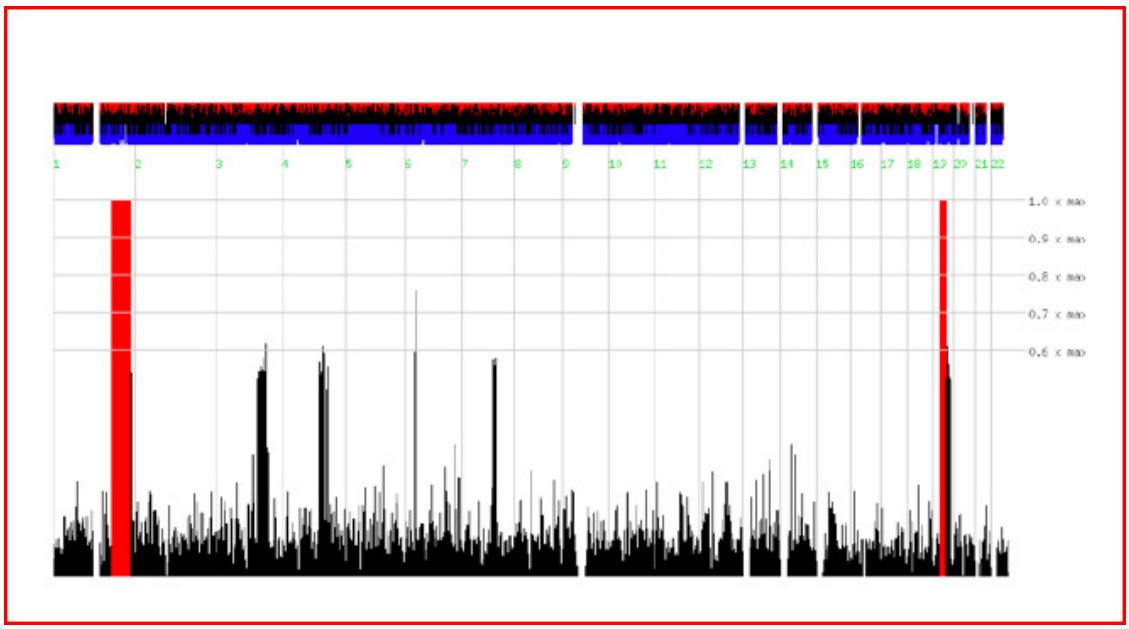


**Figure 11**: homozygosity mapping result for family 4 showing two RHOs on chromosome 1 (from position 176414781 bp to position 243261751 bp) and 19 (from position20799670 bp to position 39641146 bp).

## SUPPLEMENTARY DATA

**File 1**: list of the genes included in the homozygous area on chromosomes 2 and 17 for family 2

| C | Gene Start (bp) | Gene End (bp) | HGNC symbol | Ensembl Gene ID | Description |
|---|---|---|---|---|---|
| 17 | 28364221 | 29507664 | ACCN1 | ENSG00000108684 | Amiloride-sensitive cation channel 1, neuronal |
| 17 | 30925928 | 30929695 | PEX12 | ENSG00000108733 | Peroxisome assembly protein 12 |
| 17 | 30938395 | 31077547 | AP2B1 | ENSG00000006125 | AP-2 complex subunit beta-1 |
| 17 | 31082792 | 31094652 | RASL10B | ENSG00000141150 | Ras-like protein family member 10B Precursor |
| 17 | 31095650 | 31104010 | GAS2L2 | ENSG00000132139 | GAS2-like protein 2 (Growth arrest-specific protein 2-like 2) |
| 17 | 31112029 | 31116211 | C17orf50 | ENSG00000154768 | Uncharacterized protein C17orf50 |
| 17 | 31116989 | 31146753 | MMP28 | ENSG00000129270 | Matrix metalloproteinase-28 Precursor |
| 17 | 31160596 | 31198350 | TAF15 | ENSG00000172660 | TATA-binding protein-associated factor 2N |
| 17 | 31206073 | 31220008 | C17orf66 | ENSG00000172653 | Uncharacterized protein C17orf66 |
| 17 | 31222608 | 31231910 | CCL5 | ENSG00000161570 | C-C motif chemokine 5 Precursor |
| 17 | 31269197 | 31281893 | RDM1 | ENSG00000187456 | RAD52 motif-containing protein 1 |
| 17 | 31285638 | 31294787 | LYZL6 | ENSG00000161572 | Lysozyme-like protein 6 Precursor |
| 17 | 36332478 | 36347362 | KRT23 | ENSG00000108244 | Keratin, type I cytoskeletal 23 |
| 17 | 36368195 | 36376670 | KRT39 | ENSG00000196859 | Keratin, type I cytoskeletal 39 |
| 17 | 36387494 | 36396152 | KRT40 | ENSG00000204889 | Keratin, type I cytoskeletal 40 |
| 17 | 37808001 | 37828800 | PTRF | ENSG00000177469 | Polymerase I and transcript release factor |
| 17 | 37864388 | 37928122 | ATP6V0A1 | ENSG00000033627 | V-type proton ATPase 116 kDa subunit a isoform 1 |
| 17 | 37941477 | 37949990 | NAGLU | ENSG00000108784 | Alpha-N-acetylglucosaminidase Precursor |

| | | | | | |
|---|---|---|---|---|---|
| 17 | 37954758 | 37960750 | HSD17B1 | ENSG00000108786 | Estradiol 17-beta-dehydrogenase 1 |
| 17 | 37967618 | 37971821 | COASY | ENSG00000068120 | Bifunctional coenzyme A synthase |
| 17 | 37972604 | 37978746 | MLX | ENSG00000108788 | Max-like protein X |
| 17 | 37977881 | 37983375 | PSMC3IP | ENSG00000131470 | Homologous-pairing protein 2 homolog |
| 17 | 37985066 | 38014928 | FAM134C | ENSG00000141699 | Protein FAM134C |
| 17 | 38015220 | 38020773 | TUBG1 | ENSG00000131462 | Tubulin gamma-1 chain |
| 17 | 38064837 | 38072547 | TUBG2 | ENSG00000037042 | Tubulin gamma-2 chain |
| 17 | 38073463 | 38082495 | PLEKHH3 | ENSG00000068137 | Pleckstrin homology domain-containing family H member 3 Precursor |
| 17 | 38084946 | 38087371 | CCR10 | ENSG00000184451 | |
| 17 | 38088158 | 38105358 | CNTNAP1 | ENSG00000108797 | Contactin-associated protein 1 Precursor |
| 17 | 38105820 | 38150574 | EZH1 | ENSG00000108799 | Enhancer of zeste homolog 1 (ENX-2) |
| 17 | 38166731 | 38168585 | RAMP2 | ENSG00000131477 | Receptor activity-modifying protein 2 Precursor |
| 17 | 38178980 | 38185142 | VPS25 | ENSG00000131475 | Vacuolar protein-sorting-associated protein 25 |
| 17 | 38186222 | 38202587 | WNK4 | ENSG00000126562 | Serine/threonine-protein kinase WNK4 |
| 17 | 38203179 | 38204248 | CCDC56 | ENSG00000183978 | Coiled-coil domain-containing protein 56 |
| 17 | 38204464 | 38216179 | CNTD1 | ENSG00000176563 | Cyclin N-terminal domain-containing protein 1 |
| 17 | 38215678 | 38229807 | BECN1 | ENSG00000126581 | Beclin-1 |
| 17 | 38238949 | 38249301 | PSME3 | ENSG00000131467 | Proteasome activator complex subunit 3 |
| 17 | 38250135 | 38256248 | AOC2 | ENSG00000131480 | Retina-specific copper amine oxidase Precursor |
| 17 | 38256727 | 38263664 | AOC3 | ENSG00000131471 | Membrane primary amine oxidase |
| 17 | 38306341 | 38318912 | G6PC | ENSG00000131482 | Glucose-6-phosphatase |
| 17 | 38356073 | 38386033 | AARSD1 | ENSG00000108825 | Alanyl-tRNA synthetase domain-containing protein 1 |
| 17 | 38386108 | 38399233 | RUNDC1 | ENSG00000198863 | RUN domain-containing protein 1 |
| 17 | 38403972 | 38408482 | RPL27 | ENSG00000131469 | 60S ribosomal protein L27 |
| 17 | 38412351 | 38419998 | IFI35 | ENSG00000068079 | Interferon-induced 35 kDa protein |
| 17 | 38420148 | 38427985 | VAT1 | ENSG00000108828 | Synaptic vesicle membrane protein VAT-1 homolog |

| | | | | | |
|---|---|---|---|---|---|
| 17 | 38430784 | 38437583 | RND2 | ENSG00000108830 | Rho-related GTP-binding protein RhoN Precursor |
| 17 | 38449840 | 38530994 | BRCA1 | ENSG00000012048 | Breast cancer type 1 susceptibility protein |

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